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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/245,603	02/05/99	CURIEL D	D6080

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EXAMINER	
CLARK, D	
ART UNIT	**PAPER NUMBER**
1633	4

DATE MAILED: 04/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/245,603	Curiel
Examiner	**Group Art Unit**
Deborah Clark	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

X Notice to comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-7 and 16-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adenovirus comprising an insertion of a ligand comprising the sequence CDCRGDCFC or the FLAG octapeptide into the HI loop of the fiber protein and a method of using the said adenovirus for methods *in vitro*, does not reasonably provide enablement for an adenovirus comprising any modification of the HI loop of the fiber protein and methods of using the virus in methods *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Each claim of the instant invention requires an adenovirus having a modification in the HI loop of the fiber protein. Thus, the nature of this aspect of the claimed invention is molecular virology. The state of the art of molecular virology is fairly well developed in some aspects and not in other aspects. For instance, some viruses such as adenoviruses are fairly well characterized. However, the fiber gene of adenoviruses is not completely characterized. The fiber gene encodes the fiber protein which has three domains. The head or C-terminal domain is

thought to contain the binding region. The exact location of the binding region is not known. Further, it is not known exactly what modifications can be tolerated in this region and still allow trimerization which is necessary for internalization of the virus particle into the cell. Modifications at the genetic level in turn effects the sequence of the encoded protein which may or may not effect the folding/binding properties of the protein depending upon the particular modification. Determination of the effects of particular modifications are not predictable until they are actually made and used, hence resulting in a trial and error situation.

The instant specification teaches only 2 particular modifications to be made in the HI loop. One being inclusion of the FLAG octapeptide which is used as a label or the peptide recited above. The specification also explains the importance of not interrupting the trimerization of the fiber (see pages 6-8). It is not clear that insertions of other sequences which may effect the hydophilicity of the loop or larger sequences which could negatively effect the folding would allow trimerization.

The instant specification teaches that the claimed adenovirus is useful for gene therapy. Claims 16-22 include both *in vitro* and *in vivo* applications in the scope of the claims. Thus the full scope of the claims encompass gene therapy. Applicants have taught no reason to use the virus *in vivo* other than for gene therapy. The nature of the invention being gene therapy, the state of the prior art is not well developed and is highly unpredictable. Verma et al. states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (see Verma et al., page 239, col. 1). For instance, numerous factors complicate the

gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. [See Eck et al., ¶ bridging pages 81-82.] Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3). Sandhu et al. say that successful transfer of genes to the desired target cells does not always result in successful treatment of the disease, and go on to say that gene therapy will be most effective if the transferred genes are expressed at the correct levels and at the correct times (see Sandhu et al., page 308, col. 2). The instant specification demonstrates only gene transfer *in vivo*. The specification does not teach how to construct a therapeutic adenoviral vector, how to deliver it such that it reaches targeted cells, or that any therapeutic level of expression could be achieved to effect a therapeutic response to any particular disease.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the

breadth of the claims that it would require undue experimentation to practice the invention commensurate in scope with the claims.

3. Claims 9-15 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 9 and 10 are directed to an adenoviral vector comprising a therapeutic gene. The instant specification implies no reason to use a vector with a therapeutic gene other than to provide therapy. Claims 11-15 are directed to methods of killing tumor cells in an individual or methods of gene therapy. Claim 23 is directed to the method of claim 16, but where the adenoviral vector comprises a therapeutic gene.

For the reasons discussed above, these claims are not enabled for making and/or using without undue experimentation.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 13-23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claims 13-15 are directed to a method of gene therapy. The only step is administration of the claimed adenovirus. The claims are missing steps/elements which lead to the claimed method. The claims should conclude with a statement that indicates that the expression of the "therapeutic gene" effects a therapeutic response.

Claims 16-23 are directed to a method of increasing the ability of an adenovirus to transduce cells. The only step is a modification to the HI loop of the virus. The claims are missing the step of actually transducing cells which concludes the method such that the method claimed is actually effected.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 1-9, 16-20, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Wickham et al., US 5,846,782.

Wickham et al. teach an adenovirus modified in the HI loop by insertion of a ligand (see col. 8 lines 55 and 66) comprising the sequence CDCRGDCFC (see col. 27 and SEQ ID No. 3). Wickham et al. demonstrate an increase in the ability of the virus to transduce cells, *in vitro* (see

Table 3 in col. 36). Wickham et al. teach that the vector would preferably comprising a "passenger gene" which is desirably a "therapeutic gene" (see cols. 13-14). Therefore, the claims are anticipated.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). A computer readable form (CRF) of the sequence listing was submitted. However, the CRF could not be processed by the Scientific and Technical Information Center (STIC) for the reason(s) set forth on the attached CRF Diskette Problem Report.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825 in response to this office action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached CRF Diskette Problem Report with the reply.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Clark whose telephone number is (703) 305-4051. The examiner can normally be reached on Mondays-Fridays from 7:10 a.m. EST to 3:40 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J. CLARK
PATENT EXAMINER